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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,117	11/16/2001	Thomas L. Benjamin	00742/066002	8050

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

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6

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,117	BENJAMIN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-10 are pending in the application and under current examination.

Priority

This application is a continuation-in-part of U.S. patent application 09/812,633 and claims the benefit of priority from U.S. provisional application 60/216,723, filed 7/7/00.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other

descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

These claims are directed to *a Sal2 nucleic acid sequence* (claims 9, 10), and a method of decreasing proliferation of an abnormally proliferating cell comprising contacting said cell with *a Sal2 nucleic acid sequence* (claims 1-8), which results in the expression of a Sal2 polypeptide having tumor suppressive activity in said cells. The specification teaches, "By a *Sal2* nucleic acid sequence" as used herein is meant a nucleic acid sequence that is at least 40%, 50%, ... 95% or 99% identical to a nucleic acid sequence provided in SEQ ID No: 2 or 4 over a region comprising at least 200, 300, ... 3000 or 3500 contiguous nucleotides" (Specification, page 4, lines 21-24). Claim 3 recites "said abnormally proliferating cell has a proliferative disease-associated alteration in a Sal2 nucleic acid sequence". The specification defines, "Proliferative disease-associated alteration" as used herein, refers to any genetic change within a differentiated cell that results in the abnormal proliferation of a cell" (Specification, page 5. lines 24-25). Given the broadest reasonable interpretation, the term "a *Sal2* nucleic acid sequence" embraces a genus of sequences that is determined by its sequence homology with SEQ ID No: 2 or 4 having a length ranging from 200-3500 nucleotides; and the term "a proliferative disease-associated alteration in a *Sal2* nucleic acid" encompasses numerous (a genus of) altered *Sal2* nucleic acid molecules, which are

functionally associated with a proliferative disease. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of distinguishing characteristics and the structure-functional relationship of the genus.

The specification discloses the substitution of a Cys for the Ser at position 73 of Sal2 gene (a point mutation S73C) is associated with some of the ovarian tumors (example 7). However, the specification fails to teach the distinguishing characteristics of the genus, i.e. the members of Sal2 family, who may share only 40% sequence identity with SEQ ID No: 2, but functionally equivalent; and/or other Sal2 alterations associated with a tumor or a proliferative disease or core sequence structure whose alteration would lead to the abnormal cell proliferation. Describing a genus of molecules by sequence homology, the claims are obvious generic to a considerable number of nucleotides varying in the length of the polynucleotides, the degree of homologies among the sequences, and biological activities in any and all species of animals. With respect to claims limiting a polynucleotide by homology, even a higher percentage of homology, the functional characteristics of the resulting molecule could be significantly different. For example, one point mutation has made the normal Sal2 losing the tumor suppressive property, but the mutated sequence still shares 99% sequence homology with SEQ ID No: 1, whereas the mouse Sal2 shares about 88% sequence identify with human Sal2, yet functionally equivalent. A nucleotide sequence at 40-95% sequence homology with SEQ ID No: 2 or 4 may embrace a genus of polynucleotides that are unknown and unsequenced, and which are irrelevant to the recited Sal2. The specification fails to provide an adequate description to teach the structure-function

relationship with regard to their tumor suppressive activity, and fails to provide even one single polypeptide other than S73C mutated hSal2, thus, from the teaching of the specification, it is not possible for the skilled artisan to even guess what kind of Sal2 alteration would lead to a proliferative disease, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

The Revised Interim Guidelines state "THE CLAIMED INVENTION AS A WHOLE MAY NOT BE ADEQUATELY DESCRIBED IF THE CLAIMS REQUIRE AN ESSENTIAL OR CRITICAL ELEMENT WHICH IS NOT ADEQUATELY DESCRIBED IN THE SPECIFICATION AND WHICH IS NOT CONVENTIONAL IN THE ART" (Column 3, page 71434), "WHEN THERE IS SUBSTANTIAL VARIATION WITHIN THE GENUS, ONE MUST DESCRIBE A SUFFICIENT VARIETY OF SPECIES TO REFLECT THE VARIATION WITHIN THE GENUS", "IN AN UNPREDICTABLE ART, ADEQUATE WRITTEN DESCRIPTION OF A GENUS WHICH EMBRACES WIDELY VARIANT SPECIES CANNOT BE ACHIEVED BY DISCLOSING ONLY ONE SPECIES WITHIN THE GENUS" (Column 2, page 71436). Considering all Sal2 nucleic acids and variants from different animal species, and all possible *Sal2* alterations in various tumors and other proliferative diseases, the disclosed point mutation is not a representative species of the genus. Therefore, the specification fails to provide an adequate description to teach the structures, the identifying characteristics, and the structure-function relationship of the genus of Sal2 nucleic acids and/or altered *Sal2* nucleic acid molecules encompassed by the claims and their disease associations, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of the genus of Sal2 nucleic acid sequence or *altered Sal2* that are "associated with a proliferative disease". Therefore, only SEQ ID Nos: 2 or 4 encoding the described substitution of a Cys for the Ser at position 73 of SEQ. ID No:1 meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation

would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature and scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention without undue experimentation.

These claims are drawn to contacting cells with a genus of Sal2 associated sequence having 40-99% sequence homology with SEQ ID No: 2 or 4, wherein the cells have a proliferative disease-associated alteration in a Sal2 nucleic acid sequence. However, as indicated *supra* in the written description section, the specification fails to teach the consensus structure and/or common attribute of the genus of Sal2 and/or genus of Sal2 alterations associated with a proliferation disease, in this case, the general knowledge and levels of skill in the art do not supplement the omitted description, because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, SEQ ID Nos: 2 or 4 alone, or the substitution of a Cys for the Ser at position 73 of SEQ ID No: 1 alone is insufficient to describe nucleotide sequences encoding said genus. One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structure of polynucleotides encompassed by these claims, wherein the

resulting polynucleotide can serve as a functional tumor suppressor or associated with a proliferative disease. The skilled artisan would not know how to use the invention without first carrying out undue experimentation to determine which of the fragments of Sal2 is functionally equivalent with SEQ ID No: 1 or 3, and which of the sequence alteration, i.e. substitution, insertion, and mutation of Sal2 would lead to an abnormal cell proliferation.

Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing proliferation of an abnormally proliferating ovarian cell with a pcDNA-mSal2 *in vitro*, wherein the genome of the ovarian cell comprises a point mutation S73C in *Sal2* gene, does not reasonably provide enablement for decreasing proliferation of *any* abnormally proliferating cell *in vitro* or *in vivo* in any subject with any vector, and it does not reasonably provide enablement for decreasing the replication and dissemination of any DNA tumor virus *in vitro* or *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-5 embrace both *in vitro* and *in vivo* administration of a Sal2 nucleic acid sequence to any abnormally proliferating cell regardless whether an alteration in Sal2

gene is present and by any routes of administration using any type of nucleic acids, e.g. naked or in a vector. The claims further read on a therapeutic method, wherein administration of a Sal2 nucleic acid sequence would reduce or prevent an abnormal proliferation including tumor growth, and would reduce or prevent DNA tumor virus replication and dissemination. The specification teaches that human *Sal2* gene has been mapped to chromosome 14q12 and subsequently, this region of 14q is associated with a loss of homozygosity in 49% of ovarian cancers and about 25% of bladder cancers, "*these findings along with the underlying rationale of 'tumor host range' selection, suggest the possibility that sal2 may function as a tumor suppressor*" (paragraph bridging pages 36 and 37). The specification goes on to teach that transducing an ovarian carcinoma cell line (SKOV3) with a mSal2 (p150) expression vector (pcDNA-mSal2 expressing p150) would decrease the percentage of cells in S-phase, and 30-50% of the cells expressing p150 appeared to be apoptotic; that a colony reduction assay shows a clear reduction in viable SKOV3 cells transfected with the expression vector, reflecting both growth suppressive and apoptosis inducing activity of $p150^{sal2}$ (example 8). However, the specification fails to teach whether transfecting any abnormal proliferating cells, regardless the status of Sal2, would induce growth suppression and/or apoptosis, the routes, timing, and the means of *in vivo* administration so that the Sal2 could sufficiently reach the cells with a Sal2 associated abnormal proliferation; whether supplementing Sal2 would change the phenotype of the abnormally proliferating cells so that the a proliferating disease could be prevented or

reversed, thus, fails to provide an enabling disclosure commensurate with the scope of the claims.

Although the principle of gene replacement therapy is relatively simple, the execution of such requires sophisticated state of the art. The nature of the invention being gene therapy, the state of the prior art is not well developed and is highly unpredictable. *Verma et al* (Nat. 1997 Sep; 389:239-242) states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, col. 1). For instance, numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. *Eck et al* (Phar Basis Ther 1995; 77-101) explain, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. (Paragraph bridging pages 81-82) *Verma et al* state that one major obstacle to success has been the inability to deliver genes efficiently and obtain sustained expression (see Verma et al., page 239, col. 3). While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous

teachings available in the art. For example, *Miller* (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "NO SINGLE DELIVERY SYSTEM IS LIKELY TO BE UNIVERSALLY APPROPRIATE, FOR INSTANCE, THE REQUIREMENTS OF GENE THERAPY FOR CYSTIC FIBROSIS ARE GREATLY DIFFERENT FROM THOSE OF CANCER" (1st paragraph, page 190). "FOR THE LONG-TERM SUCCESS AS WELL AS THE WIDESPREAD APPLICABILITY OF HUMAN GENE THERAPY, THERE WILL HAVE TO BE ADVANCES...TARGETING STRATEGIES OUTLINED IN THIS REVIEW, WHICH ARE CURRENTLY ONLY AT THE EXPERIMENTAL LEVEL, WILL HAVE TO BE TRANSLATED INTO COMPONENTS OF SAFE AND HIGHLY EFFICIENT DELIVERY SYSTEMS" (page 198, column 1). *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). *Deonarain* reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). *Verma* (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). *Zink et al* (Gene Ther Mol Biol 2001 Jan;6:1-24) teach that in addition to the interaction of transcription factors with specific DNA elements, the transcription of mammalian genes and transgenes integrated into mammalian genomes is regulated at the levels of chromatin structure and nuclear architecture, "TRANSCRIPTIONAL REGULATION OF INTEGRATING GENE THERAPY VECTORS IS ONLY WELL INVESTIGATED AT THE MOLECULAR LEVEL,

FEW DATA EXIST REGARDING THE INVOLVEMENT OF CHROMATIN STRUCTURE, AND VIRTUALLY NOTHING IS KNOWN ABOUT THE INVOLVEMENT OF NUCLEAR CHROMOSOME- AND GENOME ARCHITECTURE. THEREFORE, IT IS NOT SURPRISING THAT THE EXPRESSIONAL BEHAVIOR OF GENE THERAPY VECTORS AFTER INTEGRATION IS OFTEN UNPREDICTABLE AND DIFFICULT TO IMPROVE" (abstract). The specification fails to teach which type of nucleic acids and/or vector is suitable for use in the claimed invention, how to deliver them such that it reaches targeted cells, how to overcome the art-known unpredictability, or any therapeutic level of expression could actually be achieved to affect a therapeutic response to any particular disease, thus fails to provide an enabling disclosure commensurate with the scope of the claims.

In view of the state of the art in gene therapy with tumor suppressors, p53 is a representative and well-studied example in the field. *Vinyals et al* (Gene Ther 1999;6:22-33) teach the approach of supplementing wild-type p53 (wt*p*53) into human cancer cells bearing a p53 mutation, which approach uses the same principle and strategy in treating abnormally proliferating cells as does the instantly claimed invention. *Vinyals et al* acknowledged that wt*p*53 gene expression triggers apoptosis in vitro in some transfected cancer cells, prevents colony formation in soft agar and inhibits tumor growth in nude mice, and further teach, "THE INTRODUCTION OF EXOGENOUS WILD-TYPE P53 INTO HUMAN CANCER CELLS BEARING P53 MUTATION DOES NOT NECESSARILY RESULT IN INHIBITION OF TUMOR GROWTH" (abstract), that "EACH TYPE OF NEOPLASTIC CELL OFFERS A PARTICULAR ENVIRONMENT IN WHICH WT*P*53 MIGHT GENERATE DIFFERENT EFFECTS. THUS, IF THE DIFFERENT ONCOGENE-ACTIVATED PATHWAYS DIFFERENTIALLY MODULATE THE SUPPRESSOR FUNCTIONS OF WT*P*53, THE STATUS OF THE ENDOGENOUS P53 GENE MIGHT ALSO INFLUENCE THE EFFECTS OF THE

EXOGENOUS GENE" (right column, page 22), They teach that "IN BREAST CANCER FOR EXAMPLE, SEVERAL MUTATIONS ARE FOUND IN ADDITION TO THOSE IN THE P53 GENE AND THE INDIVIDUAL CONTRIBUTION OF EACH ONE IN TERMS OF GROWTH ADVANTAGE IS STILL UNCLEAR. " (left column, page 23). In fact, in the breast cancer cell lines they investigated the introduced wt*p*53 expression was lost after several generation passages (right column, page 23), that tumorigenic phenotype is not fully suppressed in mutated p53 cell lines that express exogenous wt*p*53 (right column, page 24), that the percentage of apoptotic cells in tumors from wt*p*53 transfectant cells was low and similar, if not identical, in tumors of the parental cell lines (1st paragraph, page 25). They go on to teach, "THE FAILURE OF THIS NOVEL GENE THERAPY HAS MAINLY BEEN ATTRIBUTED TO AN INCOMPLETE TARGETING OF THE TUMOR CELL POPULATION, BUT THE IMPACT OF THE ENDOGENOUS P53 MUTATED PROTEIN AND THE GENOMIC INSTABILITY OF THE EXOGENOUS WT*P*53 GENE SHOULD ALSO BE CONSIDERED" (last paragraph, page 27) and concluded, "OUR RESULTS SHOW THAT CELLS ARE ENDOWED WITH A SPECIFIC MACHINERY THAT MAY REACT AGAINST THE EXOGENOUS WT*P*53, ABROGATING ITS INHIBITORY-GROWTH FUNCTION WITH THE PURPOSE OF ASSURING MALIGNANCY WHEN IT BECOMES COMPROMISED. THIS ABROGATION MAY BE EXERTED THROUGH DIFFERENT MECHANISMS WHICH MIGHT BE RELATED TO THOSE THAT ORIGINALLY INACTIVATED THE ENDOGENOUS GENE IN EACH CELL TYPE". These teachings are consistent with the teaching of *Tavtigian et al* (USP 6,033,857), "THE INVOLVEMENT OF SO MANY GENES UNDERSCORES THE COMPLEXITY OF THE GROWTH CONTROL MECHANISMS THAT OPERATE IN CELLS TO MAINTAIN THE INTEGRITY OF NORMAL TISSUE", "SO FAR, NO SINGLE GENE HAS BEEN SHOWN TO PARTICIPATE IN THE DEVELOPMENT OF ALL, OR EVEN THE MAJORITY OF HUMAN CANCERS" (column 1, lines 57-62).

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene replacement therapy with tumor suppressor genes for abnormally proliferative diseases, such as cancer or tumor, still recognized that such methods are neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for the claimed subject matter. Although the instant specification provides data from an *in vitro* study for supplementing Sal2 nucleic acid.(SEQ ID No: 3) to ovarian cancer cells having Sal2 S73C mutation, they are not sufficient to support the full scope of the claims.

Claims 6-8 embrace a therapeutic method for decreasing *any* DNA tumor virus replication and dissemination by contacting cells infected with a (any) DNA tumor virus with a Sal2 nucleic acid sequence, wherein the virus encompassed by the claims are wild-type or tumor host range mutants. The specification defines "DNA tumor virus" as "is meant a virus that has a mammalian host range, that can transform a normal cell into an abnormally proliferating cell, that examples of such include SV40, polyoma virus, parvovirus, papilloma virus, herpes virus, and primate adenovirus" (lines 4-8, page 4). The specification teaches a THR mutant virus TMD-25 (example 1), that the host range defect of TMD-25 is based on its inability to bind a sequence that showed strong homology to the human gene hSal2 (example 2), that mSal2 binds to large T protein of wild type but not TMD-25 mutant polyoma virus (example 3, figures 4a-b), that newborn mice inoculated with a wild-type polyoma virus would develop tumors in multiple organs whereas the TMD-25 mutant only developed fibrosarcomas at the injection site, and

showed no sign of viral replication in any of the other organs (example 4 and table 4). However, the specification is silent with regard to administering an exogenous Sal2 nucleic acid and its effect on DNA virus replication, and fails to teach how administering of a Sal2 nucleic acid sequence is related to the replication and dissemination of the TMD-25 or of any DNA tumor virus, particularly in view that the large T protein of wild type DNA tumor virus would interact with Sal2; the specification fails to provide any evidence in vitro or in vivo, that administration of a Sal2 nucleic acid sequence would decrease any DNA tumor virus replication and dissemination. Accordingly, the specification fails to provide an enabling disclosure for the claimed invention.

Therefore, in view of the quantity of experimentation necessary to determine the parameters for treatment of any and all proliferative diseases, in particular for treatment of any and all types of tumors and suppressing any DNA tumor virus replication in vivo with therapeutic Sal2 nucleic acids, the lack of direction or guidance provided by the specification, and the breadth of the claims directed to the use of numerous Sal2 nucleic acids for the treatment of any type of tumor or over-proliferation, it would have required undue experimentation for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims are vague and indefinite because the claims fail to set forth any active and positive step. The method of claims 1 or 6 calls for contacting abnormally proliferating cells or a cell infected with a DNA tumor virus with a Sal2 nucleic acids, however, there is no positive step to recite how said contacting could be done specifically in the target cells in an *in vivo* situation. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. Claim 1 is also incomplete because it provides a method of decreasing proliferation of an abnormally proliferating cell, however, there is no recitation in the body of the claim that clearly relates back to the preamble.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 22, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER